REMARKS

Claims 1-33 are currently pending in this application. Claims 7-19, 26-30 have been withdrawn from consideration.

Rejections under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 1-2, 4-6, 20-25 and 31-33 as allegedly lacking enablement. Specifically, the Examiner contends that the specification does not provide enablement for (1) the use of an "estrogen compound"; (2) how one can determine the amounts of the estrogen compounds that would decrease the levels of β peptides, but not effect soluble APP; and (3) how the invention relates to a human with Alzheimer's disease.

The Examiner's rejection is respectfully traversed. With regard to (1) and (2), Applicants respectfully submit that at the time the instant application was filed estrogen compounds were a well-known class of molecules. Furthermore, Applicants' specification describes, in detail, various estrogen compounds which may be used in the methods of the invention. (See, for example, page 8, line 6 through page 9, line 22 of Applicants' specification). In addition, Applicants' specification discloses methods for testing for estrogen compounds and for determining effective the amounts of estrogen compounds. In particular, the Examiner's attention is respectfully pointed to Examples 1, 2 and 3 of the specification. Example 3 discloses that "[t]he ovariectomized guinea pig model described in Example 1 or the overiectomized transgenic rodent model described in Example 2 can be used to screen for compounds or, more optimally, to evaluate candidate compounds obtained from screens for the ability to affect Aβ levels in the brains of these animals." See, page 29, ll. 7-11. A person of skill in the art, armed with the knowledge of these models, could easily screen for and identify estrogen compounds useful in the method of the invention, *e.g.*, estrogen compounds which would decrease the levels of β peptides, but not effect soluble APP (sAPP). For example, a candidate estrogen compound can be administered to overiectomized guinea pigs and after the treatment, brains can be collected from sacrificed animals for quantification of the Aβ40, Aβ42, and sAPPα levels using ELISA assays and quantitative immunoblotting, respectively. While such experimental procedures might be laborious, they do not constitute undue experimentation. As

described in the M.P.E.P., §2164.01, "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation," citing *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). See also *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404.

Regarding (3), the Examiner's attention is respectfully pointed to the Declaration Under 37 C.F.R. § 1.131 filed August 10, 2004 (herein "the August 10, 2004 Declaration"). The August 10, 2004 Declaration discloses:

> It is well known by persons having ordinary skill in the art that animal models can be used to determine the pharmacology of Alzheimer's disease (AD). AD is characterized by the accumulation of, *inter alia*, amyloid plaques and deposits, of which A is a major component (see specification of the '466 application, page 1, lines 11-20). A is derived by proteolytic processing of APP. *Id.* Guinea pigs are a useful animal model because their endogenous amino acid sequence of the Ą peptide is identical to the human sequence. See Johnstone, et al., "Conservation of the sequence of the Alzheimer's disease amyloid peptide in dog, polar bear and five other mammals by cross-species polymerase chain reaction analysis," *Mol. Brain Res.* 1991 Jul.; 10(4): 299-305 at 303 (Exhibit 12). Certain transgenic animals are also useful animal models because after introduction of a transgene, they too will express an amino acid sequence of the Ą peptide identical to the human sequence. Accordingly, the testing described herein supports use of the claimed invention in humans. (page 6, section "14" of the August 10, 2004 Declaration).

In view of the above, Applicants submit that the invention as set forth by the pending claims is enabled, and respectfully request reconsideration and withdrawal of this rejection.

Rejections under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 4 and 31-33 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention. In particular, the Examiner contends that it is unclear as to what the equine estrogen is conjugated with as recited in claim 4.

The Examiner's rejection is respectfully traversed. Applicants respectfully submit that the conjugated equine estrogen referred to in claims 4 and 31-33 is a well-known compound, sold commercially under the trade name PREMARIN® (Wyeth), as disclosed in Applicants' specification at, for example, page 8, lines 16-17. At the time the application was filed, PREMARIN® was well-known in the art to comprise a mixture of different estrogens which are conjugated to one another. The estrogens are not conjugated to anything else. (See, for example, U.S. Patent No. 5,719,137, cited by the Examiner in the instant Office Action, which contains a discussion of PREMARIN® at column 2, lines 18-36). Therefore, the claims, when read in conjunction with Applicants' specification, are clear and definite. Accordingly, reconsideration and withdrawal of the foregoing rejection under 35 U.S.C. §112, second paragraph, is respectfully requested.

Rejections under 35 U.S.C. §102(b)

Claims 20, 21 and 23-25 stand rejected as allegedly being anticipated by Washburn (U.S. Patent No. 5,719,137, referred to herein as "the '137 patent"). In particular, the Examiner asserts that the '137 patent discloses the use of 7 α-dihydroequilenin in a method of reducing the risk of Alzheimer's disease and other dementia related conditions in humans.

Applicants respectfully traverse the foregoing rejection for the following reasons. The '137 patent discloses the use of 7 α-dihydroequilenin for the prevention of neurodegeneration and cognitive dysfunction associated with AD and other dementia related disorders. The '137 patent describes that, in order to test the effect of 7 α-dihydroequilenin, rats are administered 7 α-dihydroequilenin and dendrite spine densities in the brains of the rats are examined. Results indicated that 7 α-dihydroequilenin has a protective effect on hippocampal CA1 region dendritic spines, an area of the brain known to be involved in cognitive functions (see column 7, lines 14-18 of the '137 patent).

Claim 20 is directed to methods for delaying or reducing the likelihood of, or ameliorating, a disease or disorder associated with amyloidosis, comprising administering an Aβ level reducing dose of an estrogen compound to a subject who has an increased risk for developing or shows a symptom of the disease or disorder associated with amyloidosis, where the dose of the estrogen compound does not affect soluble APP levels.

The '137 patent fails to teach or suggest each and every element of independent claim 20. In particular, the '137 patent does not teach or suggest administering an estrogen compound in an amount which reduces Aβ but does not affect soluble APP levels. Moreover, the '137 patent does not teach or suggest any dose of 7 α-dihydroequilenin that has any effect of 7 α-dihydroequilenin on Aβ at all, nor does it teach or suggest a dosage of 7 α-dihydroequilenin which does not affect soluble APP levels. The '137 patent only describes the effect of administering an estrogen compound on dendritic spines in the brains of rats. Therefore, the '137 does not anticipate the invention as claimed in independent claim 20. Accordingly, reconsideration and withdrawal of the foregoing rejection under 35 U.S.C. §102(b), is requested.

Claims 1-3, 5-6, 20, 21, 24 and 25 stand rejected as allegedly being anticipated by Xu et al. (Nature Medicine, vol 4, April, 1998, pp. 447-451). The Examiner contends that Xu et al. disclose that estrogen reduces neuronal generation of Aβ-amyloid peptides, in particular Aβ42, and thereby delays or prevents AD.

Applicants respectfully traverse the foregoing rejection and submit that Xu et al. fail to teach or suggest each and every element of the claimed invention. Xu et al. disclose a method for modulating expression, production, or formation *of APP* (not amyloid-β) by administering a high dose of 17β-E_2. Xu et al. provide *in vitro* data based upon rodent and human embryonic cell cultures.

Claim 1 is directed to methods for reducing a level of amyloid-β (Aβ) peptides *in vivo*, comprising administering an Aβ level reducing dose of an estrogen compound to an animal, where the animal has an increased level of Aβ, and *where the dose of the estrogen compound does not affect soluble APP levels.*

Claim 20 is directed to methods for delaying or reducing the likelihood of, or ameliorating, a disease or disorder associated with amyloidosis, comprising administering an Aβ level reducing dose of an estrogen compound to a subject who has an increased risk for developing or shows a symptom of the disease or disorder associated with amyloidosis, *where the dose of the estrogen compound does not affect soluble APP levels.*

Xu et al. disclose *modulation of APP levels* with a superphysiological dose of estrogen and does not disclose an amyloid-specific effect. Xu et al. fail to teach or suggest that estrogen can be administered in doses which do not effect soluble APP levels yet which are effective in reducing levels of Aβ peptides. In fact, Xu et al. disclose that 17β-E_2 increases soluble βAPP (see page 449, first paragraph of Xu et al.). Therefore, Xu et al. do not and can not anticipate the claimed invention. Accordingly, reconsideration and withdrawal of the foregoing rejection under 35 U.S.C. §102(b), is requested.

Rejections under 35 U.S.C. §103(a)

Claim 22 stands rejected as allegedly obvious over the '137 patent. The Examiner contends that all that is lacking in the '137 patent is administration of the estrogen compound for at least 10 days, and that it would have been obvious to one of ordinary skill in the art to administer the compound for at least 10 days.

Applicants respectfully traverse the foregoing rejection. As set forth above, the '137 patent does not teach or suggest administering an estrogen compound in an amount which reduces Aβ but does not affect soluble APP levels, as is claimed in the instant invention. Moreover, the '137 patent does not teach or suggest any dose of 7 α-dihydroequilenin that has any effect of 7 α-dihydroequilenin on Aβ at all, nor does it teach or suggest a dosage of 7 α-dihydroequilenin which does not affect soluble APP levels. Thus, the '137 patent fails to teach or suggest each and every element of independent claim 20, upon which claim 22 is dependent, and therefore does not suggest, much less anticipate, the claimed invention. See M.P.E.P. §2143. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection of claim 22 under 35 U.S.C. §103(a).

Claims 4, 22, 23 and 31-33 stand rejected as allegedly obvious over Xu et al. The Examiner asserts that even though Xu et al. lacks (1) the use of estrogens other than estradiol; (2) the use of estrogens in a controlled device; and (3) the amounts and the protocol of administration, it would have been obvious to one of ordinary skill in the art to arrive at the claimed invention.

Applicants respectfully traverse the foregoing rejection. As set forth above, Xu et al. fail to teach or suggest that estrogen can be administered in doses which do not effect soluble APP levels yet which are effective in reducing levels of Aβ peptides. Moreover, Xu et al. teach away from the present invention. In particular, Xu et al. teach that treatment with 17β-E_2 increases soluble βAPP levels, which is contrary to the surprising discovery of the instant invention that the level of Aβ peptides are reduced *in vivo* without soluble APP levels being affected. Thus, Xu et al. fail to teach or suggest each and every element of independent claims 1 and 20, upon which claims 4, 22, 23 and 31-33 are dependent, and therefore does not suggest, much less anticipate, the claimed invention. See M.P.E.P. §2143. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection of claims 4, 22, 23 and 31-33 under 35 U.S.C. §103(a).

Claims 1-6, 20-25 and 31-33 stand rejected as allegedly obvious over WO 99/48488 (herein after "the '488 publication") in combination with Washburn (U.S. Patent No. 5,510,342, hereinafter "the '342 patent"), Holland (U.S. Patent No. 3,843,662, hereinafter "the '622 patent") and Lundeen (Endocrinology, vol. 138, pp. 1552, 1997). The Examiner contends that the '488 publication teaches that blood cholesterol levels correlate with the production of amyloid protein and are predictors of populations at risk of developing AD. The Examiner also contends that the '488 publication teaches methods of lowering cholesterol, which can be used to decrease production of Aβ, thereby decreasing the risk of developing AD. The Examiner acknowledges that the '488 publication lacks the use of estrogens. Regarding the '342 patent, the '662 patent and Lundeen, the Examiner asserts that these references teach the use of estrogens for lowering blood cholesterol. The Examiner states that it would have been obvious to one of ordinary skill in the art to use estrogens in the teaching of the '488 publication for lowering the levels of Aβ peptide and decrease the risk of AD because the secondary references teach that estrogens and conjugated estrogens lower cholesterol and because the '488 publication teaches that methods of lowering cholesterol can be used to decrease production of Aβ.

Applicants respectfully traverse the foregoing rejection. In order to establish a *prima facie* case of obviousness, it is necessary for the Examiner to present evidence, preferably in the form of some teaching, suggestion, incentive, or inference in the applied references, or in the form of generally available knowledge, that one having ordinary skill in the art would have been motivated to make the claimed invention and would have had a reasonable expectation of success in making the claimed invention. Moreover, when a combination of references are used to establish a *prima facie* case of obviousness, the Examiner must present evidence that one having ordinary skill in the art would have been motivated to combine the teachings in the applied references in the proposed manner to arrive at the claimed invention. See, *e.g., Carella v. Starlight Archery,* 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986); and *Ashland Oil, Inc. v. Delta Resins and Refractories, Inc.,* 776 F. 2d 281, 227 USPQ 657 (Fed. Cir. 1985). Finally, the prior art reference or references must teach or suggest all the claim limitations. (M.P.E.P. §2143).

The '488 publication does not teach each and every limitation of the claimed invention. The '488 publication discloses that cholesterol lowering drugs can reduce production of Aβ. However, the '488 publication makes no mention of use of estrogen compounds in particular for the reduction of Aβ levels or for the treatment AD. The only examples of cholesterol lowering compounds which are disclosed in the '488 application are HMG CoA reductase inhibitors. Furthermore, the '488 application does not teach or suggest administering a dose of an estrogen compound (or any compound) which reduces Aβ levels but does not affect soluble APP levels. The '488 publication does not disclose an amyloid-specific effect of cholesterol lowering drugs, and the effects of cholesterol lowering drugs on soluble APP levels are not measured at all in the '488 publication

The '342 patent, the '622 patent and Lundeen each fail to make up for the deficiencies of the '488 publication. Each of these references discloses that certain estrogens have cholesterol-lowering effects. However, none of these secondary references teach or suggest administering an estrogen compound in a dosage which is effective in reducing Aβ levels and which also does not affect soluble APP levels. Thus, none of the cited references, either alone or in combination, teaches or suggests the claimed invention.

Furthermore, even if the cited art taught all of the claim limitations, which Applicants deny, Applicants maintain that at the time the invention was made, the prior art failed to provide sufficient motivation to modify the teachings of the primary reference to arrive at the claimed invention. The Examiner must show some objective teaching from the art that would lead an individual to combine the references, *i.e.*, there must be motivation. In particular, the mere fact that the teaching of a reference may be modified in some way so as to achieve the claimed invention does not render the claimed invention obvious unless the prior art suggested the desirability of the modification (emphasis added). See *Fritch*, *supra* and *Ex parte Obukowicz*, 27 USPQ2d 1063 (Bd. Pat. App. & Intf. 1993). The Examiner has not shown any reason why one of ordinary skill in the art would have been motivated to use an estrogen compound in an amount that is effective in reducing Aβ levels and which also does not affect soluble APP levels based on the combination of the '488 publication with the '342 patent, the '622 patent or Lundeen.

In summary, Applicants respectfully submit that, even if taken together, the cited references do not disclose or suggest the methods encompassed by the present claims. It follows that the references cited by the Examiner do not anticipate or make obvious the present invention. Reconsideration and withdrawal of the obviousness rejection is respectfully requested.

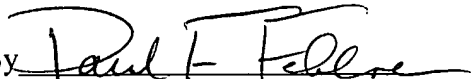
Conclusion

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited. If any points remain in issue, which the Examiner feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

Dated: March 14, 2005

Respectfully submitted,

By 

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